PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

First Named Inventor: BANDI PARTHASARADHI REDDY et al.

Serial No: 10/511,735 Group Art Unit: 1625

Filed: 10-18-2004 Examiner: CHANG, CELIA C

Att. Docket No.: H1089/20022 Confirmation No.: 2558

For: NOVEL CRYSTALLINE FORMS OF DONEPEZIL HYDROCHLORIDE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

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Sir:

INTRODUCTORY COMMENTS

Applicant(s) hereby request(s) review of the Final Rejection in the above-identified application.

No amendments are being filed with this request.

This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s) entitled Remarks/Arguments. The Remarks/Arguments section does not exceed five pages in length.

Respectfully submitted,

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December 18, 2008

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Please charge or credit our Account No. 03-0075 as necessary to effect entry and/or ensure consideration of this submission.

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REMARKS/ARGUMENTS IN SUPPORT OF THE PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action dated August 25, 2008, favorable reconsideration is respectfully requested in view of the following remarks. A Notice of Appeal in compliance with 37 C.F.R. 41.31 is filed concurrently herewith.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC § 103(a)

Claims 14-19 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over WO 97/46527 (Imai). This rejection is respectfully traversed.

The Examiner argues that (Final Office Action at pages 2-3):

> Please note that the prior art process and the instant process made: a) the same hydrated product; b) the prior art product and the instant claims have substantial similar powdered x-ray diffraction patterns . . . c) the steps are substantially similar except for the dissolving solvent which is methanol in prior art and chloroform in the instant claims. d) in examples 30-44 of the' 527 reference, a varieties of solvent were used to produce the same identical form containing about 5% water. The solvents are methanol, ethanol, tetrahydrofuran, acetonitrile; and the antisolvent to induce crystallization can optionally be used which are isopropylether, t-butylmethyl ether.

However, the claims are patentable over the '527 Imai reference because not every element of the claims is taught or suggested in the '527 (Imai) reference. The claims are drawn to a process for the preparation of donepezil hydrochloride monohydrate characterized by an x-ray powder diffraction spectrum having peaks expressed as 2θ at about 5.0, 10.0, 12.7, 13.2, 16.2, 20.0, 21.3, 23.1, 23.9 and 25.3 degrees, which comprises the steps of: a) dissolving donepezil free base in a mixture of chloroform and water; b) adding hydrochloric acid; and c) precipitating donepezil hydrochloride monohydrate from the solution formed in (b) by adding an anti-solvent.

Here, the Examiner has assumed, without providing any evidence, that the methods of producing donepezil hydrochloride in the '527 Imai reference can be altered to produce the claimed polymorph of donepezil hydrochloride monohydrate.

Different Solvents used

The '527 Imai reference discloses dissolving donepezil in methanol, addition of hydrochloric acid, and addition of t-butyl-ether. The '527 Imai reference does not disclose or suggest methods of

preparation of donepezil hydrochloride monohydrate crystalline forms by dissolving donepezil free base in chloroform/water. Clearly, these are two distinct processes, since the solvents are different (i.e. chloroform/water vs. methanol). Since the reference does not disclose or suggest this, there is no motivation to employ the process taught by the '527 Imai reference to crystallize donepezil hydrochloride monohydrate and expect to obtain the desired product to reach the limitations of the claims, with the claimed polymorphic form, and no expectation of success.

No expectation of success because use of different solvents will lead to different products

There is no basis for the assumption that different solvents can be substituted to produce the same crystalline form. The art teaches that different solvents will produce different crystalline forms of a product (see U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.), as cited in the Reply filed May 7, 2008). Clearly, these are two distinct processes, since the starting donepezil forms are different (i.e. free base vs. salt), and the solvents are different (i.e. chloroform/water vs. methanol). Therefore, the assumption that crystallization from methanol will yield the same polymorphic form as crystallization from chloroform/water has no basis in fact.

The Examiner basis the rejection on hindsight reasoning

In addition, the Examiner has based the conclusion of obviousness on hindsight reasoning. Here, the Examiner has clearly used hindsight reasoning, because as set forth in the Final Office Action (at page 3, emphasis added):

> Therefore, contrary to attorney's misinterpretation, the reference not only provided factual evidence that the same identical product was made but also suggested that variation of solvents would be an optional elements to one having ordinary skill. Although changing solvents may result in different crystalline form, in so far as crystalline donepezil hydrochloride monohydrate is concerned, variation of solvent is prima facie because the same crystalline product is made and the solvent variation is within the obviousness in operation to maintain crystalline order supported by the reference.

While it is true that, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin, 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). Here, the Examiner admits that

changing solvents may result in different crystalline form, but bases the conclusion of obviousness on the allegation that variation of solvent is *prima facie* because the same crystalline product is made. The Examiner is thus relying on the teachings of the applicant's disclosure, therefore the rejection is improper and should be withdrawn on at least this basis.

Different Products Produced

Furthermore, in addition to using hindsight reasoning to find motivation for the obviousness rejection, in fact different products are produced. The Examiner argues that the prior art product and the instant claims have a substantially similar powdered x-ray diffraction patterns. However, while the Examiner has provided a comparison of figure 1 of the '527 reference and fig. 3 of the instant application, and compares peaks of the '527 for polymorph I and the peaks of claim 14 (Office Action at page 3). However, as the Examiner admits, only seven out of the ten peaks in claim 14 are within ±0.28 of each other (see Office Action at page 3). A comparison of the XRPD pattern data shows that these are different products, because the Examiner has neglected to account for peaks at 5.0, 10.0, and 25.3 degrees 2θ. The '527 reference thus discloses a process which yields a different product. Clearly, these are two distinct processes, since the process as disclosed in the '527 reference uses different starting materials, yields a different product, and uses a different solvent, the claims are not obvious over the '527 reference. The '527 Imai reference does not disclose or suggest methods of preparation of donepezil hydrochloride monohydrate crystalline forms by dissolving donepezil free base in chloroform/water. Since the reference does not disclose or suggest this, there is no motivation to employ the process taught by the '527 Imai reference to crystallize donepezil hydrochloride monohydrate and expect to obtain the desired product to reach the limitations of the claims, with the claimed polymorphic form, and no expectation of success.

Reconsideration and withdrawal of the rejection is therefore respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 112 FIRST PARAGRAPH – WRITTEN DESCRIPTION AND ENABLEMENT

Claims 14-19 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Examiner argues that with regard to the donepezil hydrochloride monohydrate, if the employing of di-isopropyl ether and t-butylmethyl ether can be shown by factual evidence to produce "different" products, then the claims lack enabling support from the specification that "all

solvent/mixture solvent" is operable and the 112 first paragraph rejection is proper (Office Action at page 3).

However, here the Specification discloses the manner and process for making and using the claimed invention, including working examples which show the efficacy of the claimed invention. For example, Examples 4 and 5 of the Specification discloses a process of making donepezil hydrochloride monohydrate (see ¶[0053] and ¶[0054]).

Thus, given the teachings of the Specification, in light of the further experimentation carried out by Applicant using the disclosed methods, the quantity of experimentation required is not excessive in view of the subject matter of the claims. The Specification sets forth several methods for producing a monohydrate of donepezil hydrochloride, and the two novel crystalline forms of donepezil hydrochloride monohydrate. Working Examples are also provided (see Example 4 and Example 5), as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions to practice the claimed process, without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC § 102(g)

Claims 14-19 are provisionally rejected under 35 U.S.C. 102(g) as allegedly being anticipated by WO 2007/0150052 (Manikowski) which designated the US. This rejection is respectfully traversed.

The Examiner has maintained the anticipation rejection over WO 2007/0150052. The Examiner argues that if the employing of di-isopropyl ether and t-butylmethyl ether can be shown by factual evidence to produce the "same" product, then the application dates are sufficiently close as to required factual support in consideration of an interference proceeding (Office Action, paragraph bridging pages 3-4).

However, the priority date of the WO 2007/0150052 publication is July 30, 2005. The instant application, U.S. Application No. 10/511,735, is a national stage application under 35 U.S.C. 371 of PCT/IN2003/00158, filing date April 16, 2003. The United States Patent and Trademark Office in its capacity as a Designated / Elected Office (37 CFR 1.495) determined that the international application met the requirements of 35 U.S.C. 371, and was accepted for national patentability examination in the

United States Patent and Trademark Office. The filing date of the 10/511,735 application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363). Pursuant to 35 U.S.C. 363 an international application designating the United States shall have the effect, from its international filing date under article 11 of the treaty, of a national application for patent regularly filed in the Patent and Trademark Office except as otherwise provided in section 102(e) of this title. Accordingly, the '527 (Imai) reference is not a proper prior art reference under 35 U.S.C. 102(g) over the priority date of the instant application.

In addition, in the instant case, not every element of the claims is present in the '052 (Manikowski) reference. The Examiner argues that the process of example 21 of the '052 (Manikowski) reference anticipates allegedly generic claim 14 and renders the dependent claims obvious since the anti solvent employed in the example is t-bu-methyl ether which is homologous to isopropylether.

However, the claim is drawn to a process for producing a polymorphic form of donepezil hydrochloride monohydrate by dissolving donepezil free base in a mixture of chloroform and water, adding hydrochloric acid, and precipitating donepezil hydrochloride monohydrate from the solution formed by adding an anti-solvent. Therefore, in the claimed process, donepezil free base is mixed in a mixture of chloroform and water, while in contrast the '052 (Manikowski) reference discloses a process in which donepezil hydrochloride (the salt form) is dissolved in methanol. The '052 (Manikowski) reference does not disclose methods of preparation of donepezil hydrochloride monohydrate crystalline forms by dissolving donepezil free base in chloroform/water. Clearly, these are two distinct processes, since the solvents are different (i.e. chloroform/water vs. methanol). Since the reference does not disclose this, the '052 (Manikowski) reference cannot be an anticipatory reference over the claimed method.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

* * *

Accordingly, the Pre-Appeal Brief Conference Panel is respectfully requested to withdraw the appealed rejection(s) and pass this application on to issuance.